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## Regulatory Paternalism in the Market for Drugs: Lessons from Vioxx and Celebrex

Richard A. Epstein, LL.B.\*

### INTRODUCTION: RUMBLINGS OF DISCONTENT

The trials and tribulations of the pharmaceutical industry made front-page news in the Fall of 2004. On September 30, 2004, Merck & Co. announced that it would voluntarily pull its Cox-2 inhibitor, Vioxx, from the market.<sup>1</sup> To say the least, the decision to take the drug off the market caused no little stir. Vioxx, which had entered the market with great fanfare in 1999, had become an instant blockbuster drug with over one hundred million prescriptions,<sup>2</sup> twenty million users,<sup>3</sup> and about \$2.5 billion in annual sales.<sup>4</sup> The success of the drug paralleled that of two Pfizer Cox-2 inhibitors, Celebrex and Bextra.<sup>5</sup> The success of all

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1. Barnaby J. Feder, *Criticism of Drug May Leave Pfizer Awash in Lawsuits*, N.Y. TIMES, Dec. 18, 2004, at C1; see also Anahad O'Connor & Denise Grady, *Pfizer and Celebrex: The Patients' Problems May Send Many Patients Back to Age-Old Aspirin*, N.Y. TIMES, Dec. 18, 2004, at C1.

2. Andrew Leckey, *Prognosis Is Cautious for Merck Shares, Analysts Say*, CHI. TRIB., Nov. 7, 2004, at C8.

3. Theresa Agovino, *Lawsuits Threaten Health of Merck; Vioxx Litigation May Cost Billions*, CHI. TRIB., Nov. 8, 2004, at A1. The article estimated that potential tort liability could amount to \$17.6 billion over the next decade.

4. Leckey, *supra* note 2.

5. For the FDA's cautious position on the decision to take Vioxx off the market, see FDA, Vioxx (rofecoxib) Questions and Answers, Question 12, at <http://www.fda.gov/cder/drug/infopage/vioxx/vioxxQA.htm> (Sept. 30, 2004) (noting that "[t]he results of clinical studies with one drug in a

three drugs is (or at least, was) attributable to their apparent ability to satisfy the best of both possible worlds by relieving pain without provoking the risk of stomach or intestinal bleeding inherent to ibuprofen and similar drugs. The number “2” appended to the term Cox, with respect to drugs such as Vioxx, signified a welcome measure of specificity.<sup>6</sup> Drugs in this family could work effectively where needed without causing disruption where they were not wanted. Indeed, Merck had such confidence in the ability of Vioxx to specifically target its effects that the company was seeking to expand the portfolio of permissible uses by raising the dosage to determine the effectiveness of Vioxx in treating polyps—intestinal growths that could become cancerous. However, during these trials, Merck discovered in its own clinical data an apparent increase in the number of negative cardiovascular occurrences, which, if extrapolated, “may” suggest that as many as 27,000 persons had died from the use of the product.<sup>7</sup>

Merck’s decision to withdraw the drug from the market took place before the FDA made any such demand,<sup>8</sup> which of course leaves open the possibility that the drug could be returned to the market without a new round of FDA approvals. The common folk wisdom in the litigation industry suggests that a voluntary removal plays much better before a jury in subsequent litigation than a forced removal after a prolonged FDA hearing, which is closer to the situation with the diabetes drug, Rezulin.<sup>9</sup> Yet in this instance, Merck’s action seems to have had the opposite effect. The decision to take Vioxx off the market was widely read as a fatal admission of dangerous conduct by a firm that should never have made the launch in the first place. The veritable firestorm of reactions included the anticipated onslaught of ordinary tort actions for personal injuries buttressed by congressional investigations, inquiries by the Securities and Exchange Commission, derivative actions, suits for refunds, internal inquiries, and so

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given class do not necessarily apply to other drugs in the same class. All of the nonsteroidal anti-inflammatory drugs (NSAIDs) have risks when taken chronically, especially of gastrointestinal (stomach) bleeding, but also liver and kidney toxicity.”).

6. See Andrew Pollack, *New Scrutiny of Drugs in Vioxx’s Family*, N.Y. TIMES, Oct. 4, 2004, at C1 (“There are two forms of COX, and one of them, COX-1, helps protect the stomach lining from acids. The older drugs block both forms, which is why they cause ulcers and gastrointestinal complications that have been estimated to result in 7,500 to 16,500 deaths a year in the United States. The COX-2 inhibitors, as their name implies, block COX-2 much more than the stomach-protecting COX-1.”).

7. Leckey, *supra* note 2; see also Bruce Japsen, *Merck Withdraws Arthritis Drug; Vioxx Increased Danger to Heart*, CHI. TRIB., Oct. 1, 2004, at C1.

8. See FDA, Vioxx (rofecoxib) Questions and Answers, *supra* note 5.

9. See discussion *infra* notes 67-69 and accompanying text.

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forth.<sup>10</sup> Merck shares lost \$12 from \$45.07 to \$33 the day it announced that it would take Vioxx off the market, only to stabilize in the \$29-\$33 range thereafter.<sup>11</sup> Merck is now thought to be a potential merger target, and its board of directors has offered some 230 of its most senior managers special bonuses that will be triggered if either the company is taken over by another firm or if some other firm acquires twenty percent of its outstanding shares.<sup>12</sup> This episode prompted sharp criticisms by independent corporate watchdogs who treated it as yet another blunder by a weak Merck board.<sup>13</sup>

When Vioxx was taken off the market, the attention quickly turned to Celebrex and Bextra. Celebrex, which enjoyed a somewhat larger market share than Vioxx with about twenty-six million users generating at present some \$3.3 billion in annual sales, had not been linked to any elevated risk of heart exposure. It was not spared from the criticism, however, that it too would be shown to possess the same or similar risks as Vioxx.<sup>14</sup> On December 17, 2004, the other shoe dropped when Pfizer announced that one of two clinical studies on Celebrex revealed that it presented an elevated risk of heart attacks.<sup>15</sup> The clear implication

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10. See, e.g., Alex Berenson, *Merck's Board Appoints Panel To Investigate Handling of Vioxx*, N.Y. TIMES, Dec. 8, 2004, at C6. The inquiry does not have a termination date, nor is it clear that the special committee will publish its results. *Id.*

11. Barnaby Feder, *Merck's Actions on Vioxx Face New Scrutiny*, N.Y. TIMES, Feb. 15, 2005, at C1.

12. See Alex Berenson, *Merck Offering Top Executives Rich Way Out*, N.Y. TIMES, Nov. 30, 2004, at A1.

13. *Id.* One recent story lamenting the decline sums up the fiasco with the title "Not Everybody Loves Raymond," referring to the controversy surrounding Raymond V. Gilmartin, Merck's Chairman since 1994. Alex Berenson, *Not Everybody Loves Raymond*, N.Y. TIMES, Dec. 15, 2004, at C1.

14. See, e.g., *Arthritis Drug Worries*, CHI. TRIB., Oct. 17, 2004, at C7; Feder, *supra* note 11 (noting slumping sales of Celebrex and Bextra, even in the absence of clear proof of cardiac risks from normal dosages).

15. See FDA, Statement on the Halting of a Clinical Trial of the Cox-2 Inhibitor Celebrex (Dec. 17, 2004), at <http://www.fda.gov/bbs/topics/news/2004/new01144.html>. The statement noted the following:

The Food and Drug Administration (FDA) learned last night from the National Cancer Institute (NCI) and Pfizer, Inc., that NCI has stopped drug administration in an ongoing clinical trial investigating a new use of Celebrex (celecoxib) to prevent colon polyps because of an increased risk of cardiovascular (CV) events in patients taking Celebrex versus those taking a placebo.

Patients in the clinical trial taking 400 mg. of Celebrex twice daily had a 3.4 times greater risk of CV events compared to placebo. For patients in the trial taking 200 mg. of Celebrex twice daily, the risk was 2.5 times greater. The average duration of treatment in the trial was 33 months.

of the second finding is that the higher incidence of adverse cardiovascular events might be found in all Cox-2 inhibitors, not just Vioxx. As of this writing, Pfizer has not taken Celebrex off the market in light of the unresolved issues surrounding the inconsistent results from the various clinical trials, but it has stopped consumer advertising of the drug. The reports of lawsuits and the renewed popularity of aspirin (notwithstanding its high incidence of gastrointestinal side effects, particularly in people taking large amounts for extended periods) sent the value of Pfizer stock plunging<sup>16</sup> and raised editorial calls for both the FDA and Pfizer to think hard about whether it is best to “yank” Celebrex from the market now that Vioxx has been pulled.<sup>17</sup>

Vioxx is not the only high-profile drug to have been withdrawn from the market. A similar fate awaited the Warner-Lambert (now Pfizer) drug Rezulin, which was voluntarily withdrawn, albeit with severe FDA pressure, from the market in 2000, three years after its launch.<sup>18</sup> Rezulin’s strength lay in its ability to attack diabetes differently from drugs previously in use, but post-marketing data detected an increase in liver complications, including sixty-three cases of liver failure. The actual record is filled with various factual disputes about the frequency and severity of side effects. At the conclusion of the 1999 FDA hearings on the matter, the FDA recommended that the drug not be used as an initial therapy for diabetes but only as a second line treatment, and then in conjunction with other drugs.<sup>19</sup> A year later, Pfizer withdrew Rezulin from the market after David Willman of the *Los Angeles Times* published an exposé in which he denounced Rezulin as a “killer drug.”<sup>20</sup> Rezulin’s withdrawal precipitated a number of lawsuits, including not only actions for personal injury or death attributable to the drug, but also actions by individual consumers and

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A similar ongoing study comparing Celebrex 400 mg. once a day versus placebo, in patients followed for a similar period of time, has not shown increased risk.

*Id.* For front page stories on the fast-breaking events, see Feder, *supra* note 1; Gardiner Harris, *Pfizer and Celebrex: The Overview; Drug Trial Finds Big Health Risks in 2nd Painkiller*, N.Y. TIMES, Dec. 18, 2004, at A1; Bruce Japsen, *Heart Risks Found From Celebrex*, CHI. TRIB., Dec. 18, 2004, at C1; and O’Connor & Grady, *supra* note 1.

16. See Feder, *supra* note 1; O’Connor & Grady, *supra* note 1.

17. Editorial, *New Doubts About Celebrex*, N.Y. TIMES, Dec. 18, 2004, at A18.

18. For a fuller summary of the relevant events discussed in this paragraph, see *In re Rezulin Prods. Liab. Litig.*, 210 F.R.D. 61, 62-64 (S.D.N.Y. 2002) (denying the motion to certify a class).

19. *Id.* at 63.

20. David Willman, *The Rise and Fall of the Killer Drug Rezulin*, L.A. TIMES, June 4, 2000, at A1; see also David Willman, *Researcher’s Fees Point to Other Potential Conflicts at NIH*, L.A. TIMES, Jan. 28, 1999, at A5; David Willman, *Scientists Who Judged Pill Safety Received Fees*, L.A. TIMES, Oct. 29, 1999, at A22.

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third party payers to recover the sums paid to acquire the drug in the first place.<sup>21</sup>

The stakes involved in these withdrawals of drugs from the market, whether voluntary or mandated, are enormous.<sup>22</sup> From the point of view of the patient, if the recalls are correctly executed much needless suffering may be avoided. But if useful drugs are withdrawn with no substitutes, needy patients are deprived of another weapon in their arsenal against disease and misfortune. The stakes are every bit as large institutionally. Institutional actors are not only affected by the litigation that withdrawals spawn. The drug manufacturer also suffers the reputational losses of withdrawals; the medical profession and the pharmaceutical industry face added scrutiny;<sup>23</sup> and the FDA, the tort system, and the securities markets bear the reverberations of the decisions.

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21. I see little benefit to the use of the tort system. For a discussion of some of the liability issues, see *Wakefield v. Warner-Lambert Co.*, No. 99,086 (Okla. Civ. App. July 20, 2004) (upholding a wrongful death verdict of \$1,500,000 in compensatory damages and \$10,000,000 in punitive damages). It was notable that the decedent had died from hemolytic anemia; the claim was that the decedent could not fight off the condition because his liver function had been impaired by Rezulin. The court upheld the decision not to allow the “comment k” defense, see RESTATEMENT (SECOND) OF TORTS § 402(A) (1964), on the ground that adequate warnings were only a defense in cases of “exceptional products,” see, e.g., *Hill v. Searle Labs.*, 884 F.2d 1064, 1069 (8th Cir. 1989). The court did not address the admitted fact that the decedent had had five similar incidents before taking Rezulin. The punitive damages were said to relate to the general distribution of the drugs and the profits it generated. Other similar cases are scheduled for trial. The hostile, chilly reception to out-of-state defendants in state court should be evident. Note that I have worked with Pfizer on some Rezulin cases, but only became involved in this one in connection with a petition for certiorari to the Supreme Court.

It is worth noting that the cost-internalization arguments of product liability cut both ways. False attributions of liability lead to the unwillingness to introduce new drugs into the market at the same time that so may drug industry critics deplore the emphasis on so-called me-too drugs. See Arnold Relman & Marcia Angell, *America's Other Drug Problem: How the Drug Industry Distorts Medicine and Politics*, THE NEW REPUBLIC, Dec. 16, 2002, at 27. For a defense of me-too drugs, see Thomas H. Lee, “Me-Too” Products—Friend or Foe?, 350 NEW ENG. J. MED. 211 (2004). For my critique of Relman and Angel, see RICHARD A. EPSTEIN, DOES AMERICA HAVE A PRESCRIPTION DRUG PROBLEM?: THE PERILS OF IGNORING THE ECONOMICS OF PHARMACEUTICALS 1 (Inst. for Pol’y Innovation, Issue Brief, 2004).

22. Withdrawal from the market refers to the ability to sell new drugs. In addition, once a drug has been withdrawn those units already in the marketplace may also be recalled. Withdrawal and recall are clearly complementary strategies.

23. For two denunciations, see MARCIA ANGELL, THE TRUTH ABOUT THE DRUG COMPANIES: HOW THEY DECEIVE US AND WHAT TO DO ABOUT IT (2004); and JEROME P. KASSIRER, ON THE TAKE: HOW MEDICINE’S COMPLICITY WITH BIG BUSINESS CAN ENDANGER YOUR HEALTH (2004). For my critical review of both books, see Richard A. Epstein, *Pharma Furor*, LEGAL AFF., Jan./Feb. 2005, at 60.

In sorting out the various consequences of asserted drug failure, two interrelated questions are decisive: Which drugs should be let on the market in the first place? And which ones should be taken off? The ferocious public attacks in the Vioxx, Celebrex, and Rezulin cases are well encapsulated in this gloomy assessment offered by *The Lancet* after Vioxx was taken off the market:

[D]rug regulators must now reassess the safety and efficacy thresholds required for the licensing of a new pharmaceutical product. Clearly, this is an immensely complicated equation involving, among other factors, the nature of the condition being treated, the therapeutic strategies already available, and the perceived benefit-to-hazard ratio of the new treatment. The Vioxx story is one of blindly aggressive marketing by Merck mixed with repeated episodes of complacency by drug regulators. We need clear statements from all parties in this sorry tale about the lessons to be learned. Without more vigilant drug regulation in the future, doctors will continue to be misled and patients' lives will continue to be endangered.<sup>24</sup>

The controversy over the usage of dangerous drugs has now reached a fever-pitch, which is all the more reason to step back for a moment from the dramatic incidents of these and similar cases to develop a coherent framework to decide whether the critics of both the pharmaceutical industry and the FDA are right. That question in turn requires that we consider *two* alternatives to the status quo. The first is that we tighten up the system of regulation, both before drugs are released into the market place and after they are in common use. The second is that we *relax* the use of state regulation in *both* the prior approval and recall scenarios. The latter position has received little support in polite company, but, on balance, it has much to commend it.

This Article addresses two interlocking issues. Part I develops a simple model to determine which drugs should be released into the marketplace and why. Its central point is that the inherent *heterogeneity* in all populations cuts strongly in favor of a relaxation in the standard of pre-market approvals, as is urged in a recent paper by Malani and Hu.<sup>25</sup> The regulator who works upstream of the physician and patient lacks any knowledge of individuated circumstances that should rationally influence the decision of which drug, if any, to take, and in what dosage. So long as physicians and patients have some skill in locating the patient's position in the distribution, there is no reason to rely on the upstream

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24. Editorial, *Vioxx: An Unequal Partnership Between Safety and Efficacy*, 364 THE LANCET, 1287, 1288 (2004) [hereinafter *Vioxx: An Unequal Partnership*]; see also Eric J. Topol, *Good Riddance to a Bad Drug*, N.Y. TIMES, Oct. 2, 2004, at A15 (criticizing the use of Rezulin because of its increased risk of heart attack or stroke, from 1.9% to 3.5%).

25. Anup Malani & Feifang Hu, *The Option Value of New Therapeutics* 1 (Oct. 25, 2004) (unpublished manuscript, on file with the author).

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averages that the FDA uses. Patients and physicians should be allowed to incorporate downstream knowledge into their decisions. As far as I can tell, there are no substantive provisions in the current legislation, with its mandates that drugs be both safe and effective, that prevent the FDA from considering the variation in responses across individuals in setting the appropriate standards for decision. In light of this basic situation, Part II then argues that this model should carry over to questions of withdrawal and recall of drugs from the marketplace, either by government mandate or firm decision. So long as individual users have acquired knowledge of their personal benefits and side effects of particular drugs, companies should be reluctant to pull drugs from the marketplace, and the government should be cautious in ordering them off.

Accordingly, something is sadly amiss in dealing with the regulatory framework on prescription drugs. On this critical issue, the FDA should use its power to keep drugs from the market or to withdraw them from it with far greater caution than it does today. Often, it relies on cost-benefit analyses that can only be termed, at best, tentative and, at worst, primitive. Its entire effort to make better judgments on what treatments should be used and why smacks of an unthinking paternalism that reveals its own institutional shortcomings, as well as those of its critics who plump for stricter regulation.

Looked at in the broad scheme of things, the entire regulatory apparatus today suffers from an excess of ambition. The FDA has a critical role to fulfill in keeping counterfeit and bogus drugs off the market. It should deal harshly and effectively with fraud. But when the question turns to whether individual physicians and consumers have sufficient information to make appropriate choices, it enters into a vast swamp through which it cannot find a consistent path. In its effort to protect ordinary patients from error, it probably makes more errors than it guards against because it lacks both the particularized knowledge and the strong incentives to get matters right that ordinary people bring to their own affairs. In this area, the cure is frequently worse than the disease. The problems of error and bias that have been so frequently identified are real, but they are not avoided by the FDA or the tort system, which have additional difficulties of their own.<sup>26</sup> Here is yet another case where the administrative agency should do the unproblematic task well—deal with purity and fraud—while showing a bit of caution in making judgments for others on matters of

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26. See generally HEURISTICS AND BIASES: THE PSYCHOLOGY OF INTUITIVE JUDGMENT (Thomas Gilovich et al. eds., 2002); JUDGMENT UNDER UNCERTAINTY: HEURISTICS AND BIASES (Daniel Kahneman et al. eds., 1982). With these, contrast GERD GIGERENZER ET AL., SIMPLE HEURISTICS THAT MAKE US SMART (1999); and Gerd Gigerenzer, *Bounded Rationality: Models of Fast and Frugal Inference*, 133 SWISS J. ECON. STAT. 201 (1997). The titles reveal everything about the differences in approach.



safety and effectiveness. Protection against fraud is one thing; paternalism, whether or not intended, is quite another.

All this uneasiness about drug safety still leaves open the question of who should assemble all the information that surrounds the use of any standard drug even when fraud and misbranding are not at issue. At this point, however, there is no reason to place trust in a government monopoly, especially one that has shown itself to rate false positives (letting drugs that should be kept off the market onto the market) more highly than false negatives (keeping drugs off the markets that should be allowed). Since warnings are not coercive but informative, there is no need for a government monopoly. Private organizations can issue their own findings, and, if need be, other rating organizations can rate the various organizations that supply the data. The obvious point that individual patients, and often their physicians, are unable to assemble the needed data explains why we need third-party involvement. It does not, however, justify another government monopoly.

## I. INITIAL DRUG APPROVAL

### *A. Downstream, Not Upstream*

Although both the Rezulin and Vioxx cases focused on withdrawal and recall, those business and FDA decisions were clearly dependent on the judgments made in the initial approval process. The less risk-averse the FDA runs that initial process, the more likely it is that poor drugs will slip through the net and the greater the likelihood that dramatic business, regulatory, and litigation responses will come with the first signs of adverse events. The more stringent the initial regulatory process, the more likely it is that fewer poor drugs will slip through the net and hence the pressure for drug withdrawals and recalls will be reduced. The casual analyst might conclude, therefore, that more caution is in order at the first stage. But the error of that position is seen quickly enough by putting forward this simple proposal at the extreme: Avoid all problems with withdrawals and recalls by allowing *no* new drugs to reach the market. That conclusion would not even make perfect sense in a world in which all drugs had a negative expected value, so long as individual users who would benefit from the use of the drug can self-select. That conclusion, however, makes even less sense in the current world, where many drugs that enter the market perform as well, or even better,<sup>27</sup> than was expected on their launch. Stated otherwise, if all

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27. Such was the situation with Norvir, an Abbott anti-AIDS drug, which was found to be more effective if used in combination with other pharmaceuticals when it could be taken in lower dosages. Abbott raised its prices for the drug and was faced with threats of losing its patent rights

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drugs had a positive expected value in use on launch, then none should be kept off the market. But the obvious concern that spurs FDA involvement is that we cannot live in that Nirvana either. Drugs can kill, and if they do, no amount of damages will restore the victims and their family to the status quo ante. Nor will the deterrent effect of damages work well if the suppliers of new drugs are fly-by-night operations that are able to liquidate or go bankrupt in the short term so as to be unavailable, perhaps years later, to answer for their original defaults. Criminal sanctions are available, but are subject to high standards of proof that are unlikely to play a role in most cases.<sup>28</sup>

A system of prior restraint, then, is in principle permissible to deal with this problem, but it is not one for which private law enforcement provides much traction. Private injunctions work tolerably well, for example, in land use cases in which one party pollutes the land of his or her neighbor, but they falter when pollution from multiple sources damages many separate individuals. At this point the sensible approach has the state intervene as the agent for the aggrieved parties. But the hard question still remains: How do we know with any particular drug application whether the exercise of that permit power benefits the individual members of the public whom it is supposed to protect? Once it is recognized that there are two kinds of error—letting drugs on the market too quickly and keeping them off for too long—then someone has to decide which error is larger for which application. This task is by no means simple, even if we ignored the standard litany of public choice concerns about how individual interest groups can capture public agencies and turn them to private advantage—a risk that is as great with a consumer advocacy group, such as Public Citizen, as it is with any pharmaceutical company.<sup>29</sup>

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under the Bayh-Dole Act, which allows for march-in rights in limited circumstances. See 35 U.S.C. § 203 (2000). But the statutory claim proved weak and the flap was short-lived. See *Abbott Laboratories Comments at NIH Public Meeting Regarding Norvir and Bayh-Dole March-in Provisions*, PR NEWswire ASS'N, May 25, 2004; Bruce Japsen, *Abbott AIDS Drug Pricing Leads to Review of Patent*, CHI. TRIB., May 21, 2004, at C1; Bruce Japsen, *Abbott Defends Price Boost on AIDS Drug at U.S. Hearing*, CHI. TRIB., May 26, 2004, at C1. Note that it is critical to allow for these price increases lest the manufacturer start with a high price that retards usage unnecessarily. To take the contrary position is no better than arguing that a landlord cannot raise rentals after the original rents are set.

28. See 21 U.S.C. §§ 331, 333 (2000) (misbranding).

29. The calculus of influence is very complicated, but size and resource base are surely not the sole determinants. An individual firm with huge assets is vulnerable to legislative threats of regulation and taxation and its credibility is always suspect relative to that of independent public interest organizations that have no direct financial interest in a particular issue, but strong ideological commitments. No private firm could get away with the assertion that it is proper to ignore present value calculations in determining the costs of new products, but Public Citizen has

*B. Enter Heterogeneity*

One key step in this complex process of social control is to develop a sound set of norms that indicate which form of government action is appropriate at which stage and why. In dealing with this question, Malani and Hu start off by noting that the “[FDA] employs a simple decision-rule when deciding whether to approve a new drug for use by physicians: The average treatment effect of the new drug must be superior to the average effect of a placebo.”<sup>30</sup> Both safety and efficacy fit into this equation. Yet, as Malani and Hu immediately point out, this rule is flatly incorrect the moment that one takes into account the ability of physicians and patients to exploit the heterogeneous responses to the drug in question.<sup>31</sup> Every natural population has a variance whose essential features frequently can be captured in a normal distribution, that is, a bell-shaped curve, with a peak in the middle and a symmetrical distribution around it. Whether we think of height, eye color, lactose tolerance, or any of a million human traits, it is now indisputable that small genetic variations can lead to very large differences in observed behaviors or physical types.<sup>32</sup> We know that human responses to drugs also conform to this pattern. Some people will do better with given drugs than others. The explanation could stem from a thousand causes: age, sex, race,<sup>33</sup> and the like. Assembling a comprehensive list of the relevant factors and assigning weights to them is probably beyond the capacity of modern epidemiological science. Finding the width of the variation is also no easy task, for there is no reason to suppose that it is uniform for all medications and all populations. The question is what to make of this indisputable but incomplete

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made just that claim. See PUB. CITIZEN, AMERICA’S OTHER DRUG PROBLEM: A BRIEFING BOOK ON THE RX DRUG DEBATE 46 (2002), <http://www.citizen.org/rxfacts>. For a contrast, see the more careful empirical study, Joseph A. DiMasi et al., *The Price of Innovation: New Estimates of Drug Development Costs*, 22 J. HEALTH ECON. 151 (2003) (using an eleven percent discount rate).

30. Malani & Hu, *supra* note 25, at 1.

31. *Id.*

32. The most dramatic illustration comes from the observation that human beings and mice share virtually all their genes. It is a losing proposition to argue that the differences between them must be small, when we know otherwise, because their gene pools are the same. What is needed is some explanation as to how differences in gene expression are powerful enough to explain the observed differences. For a popular account, see Matt Ridley, *The DNA Behind Human Nature: Gene Expression and the Role of Experience*, 133 DAEDALUS 89 (2004).

33. See, e.g., Sally Satel, *Race and Medicine Can Mix Without Prejudice: How the Story of BiDil Illuminates the Future of Medicine*, MED. PROGRESS TODAY, Dec. 10, 2004, at [http://www.medicalprogresstoday.com/spotlight/spotlight\\_indarchive.php?id=449](http://www.medicalprogresstoday.com/spotlight/spotlight_indarchive.php?id=449). The original study was published by Anne L. Taylor et al., *Combination of Isosorbide Dinitrate and Hydralazine in Blacks with Heart Failure*, 351 NEW ENG. J. MED. 2049 (2004). See also Sally Satel, *I Am a Racially Profiling Doctor*, N.Y. TIMES, May 5, 2002, § 6, at 56.

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proposition?

In approaching this question, here is one initial benchmark: The variance in outcomes should be the dominant determinant in dealing with this decision. The higher the variance, the greater the gain that comes from learning where any particular individual is located on the curve in question. The FDA rule that looks only at the means of the placebo and the drug population systematically suppresses all reference to those variations, and it is modestly worrisome that the question of variance was *not* one of the factors referred to in *The Lancet* editorial, nor as far as I can tell, in any other editorial.<sup>34</sup> In practice, this effect is softened somewhat because of the ability to seek marketing approval for some discrete subpopulation that becomes the subject of a Phase II or Phase III clinical trial. But even that concession does not fully meet the problem. Even if the drug company can target in advance the group for which the drug is appropriate, which is a large question, any variation within that designated class is ignored. Consequently, a drug that does not meet the overall standard will be excluded from the market even if it works for some subpopulation. In addition, the drug will not be available for individuals outside the test population for whom it may work. Ideally, if there are some people for whom the new drug works better than a placebo and some for whom it does not, then by all means those who profit from the drug should take it while those who do not should avoid its use. But that desirable result can be reached only by allowing a drug that flunks the FDA standard to enter the market. Indeed, the greater the variation in response, the higher the return to the individual valuations, both within and across subpopulations. There will, in fact, be many cases where the average person does worse on the drug than on the placebo, but so what? All that proves is that a smaller fraction of the population can profit from the drug. It does not prove that the drug has no social value. The ban then becomes a blunt instrument because it does not separate out good from bad applications of the drug in question. In principle it is better to start dosages at the low end of the range and to increase them in light of the full range of individual responses.

The argument, however, is still more complicated than this simple version implies, for there is no guarantee that anyone will be able to determine with assurance *which* individuals could profit from the drug, *which* are not affected much one way or the other, and *which* are hurt by its use. If it turned out that no one had any indication in advance as to the effect that the drug had on him or her, the expected value of the drug declines because of the inability to route it to the right people. But even here, it does not necessarily follow that it should be kept from the market. People with very serious conditions might wish to throw the

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34. It was not mentioned, for example, in *Vioxx: An Unequal Partnership*, *supra* note 24, nor in Topol, *supra* note 24.

“Hail Mary” pass because they have nothing to lose from an adverse reaction to the drug. But, they have much to gain from the random possibility that the new treatment will work where all other treatments have failed, which explains why some drugs are approved only as “second-line” or “third-line”—for use when other interventions have failed.

This last question is but one way of saying how difficult it is to introduce standardized measures of the expected benefits that flow from a positive drug use. Indeed, this same problem recurs in multiple forms. For example, suppose the adverse consequence of a given drug treatment is instant death and the positive effect is a modest reduction in some allergic reaction; then no one wants to take the risk that he falls on the wrong side of the distribution. For example, the antibiotic chloramphenicol is seldom used because of a low incidence of fatal aplastic anemia, but it remains on the market for situations in which it may be life-saving.<sup>35</sup> But the very starkness of that illustration may, paradoxically, remove the need for a ban so long as the firm is required to reveal publicly both the probability and magnitude of all effects to the extent that these statistics have been acquired through either animal or clinical tests. In the extreme case just mentioned, the disclosure requirement will be a death knell to any efforts to market the drug at all. Even without a ban, there is little risk that any drug company will want to put forward hydrogen cyanide as a new wonder cure. Nor would liability be much of an issue either. No one would use the drug because its negative payoffs would dominate everyone’s decision, no matter what their place in the overall distribution.

Yet most cases do not have that stark profile. Oftentimes, the drugs in question are given to very sick or debilitated individuals whose prognosis for palliation or cure is dim. In some cases, there will be people who can tolerate a drug well, while others cannot. The point here is that it is routinely possible in most cases to develop some signs—indications or contraindications—which supply people with at least a rough idea of where they stand with respect to a particular drug use. Every warning label contains a list of that sort and the FDA itself maintains a drug information site that provides “information about the products we regulate.”<sup>36</sup> To the extent that individuals or their physicians have reliable information, the case for keeping the drug off the market is far weaker

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35. See, e.g., *Salmon v. Parke, Davis & Co.*, 520 F.2d 1359, 1361 (4th Cir. 1975) (“Chloromycetin, Parke, Davis’ trade name for chloramphenicol, is a potent, broad-spectrum antibiotic. Properly administered, it is a valuable, life-saving drug that can effectively treat stubborn infections. But it can be injurious—even fatal—if its use is not carefully monitored. According to the Food and Drug Administration, its most common, serious toxic effect is the development of anemia.”).

36. See Ctr. for Drug Evaluation & Research, FDA, Information About the Products We Regulate, at <http://www.fda.gov/cder/drug> (last visited Feb. 14, 2005).

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than it is if no such knowledge is available. Information of this sort is certainly available in most cases. Most drugs, like the Cox-2 inhibitors or the statins, which are used to control cholesterol, fall into distinct classes that offer some advance warnings as to which individuals are likely to gain or suffer most from a treatment. In addition, in most cases it should be possible to start individuals on low dosages of products and observe whether the beneficial effects outweigh the unpleasant side effects. Where the drug has some positive effects then the dosage might be cautiously increased, keeping a watchful eye for dose-sensitive side effects. Yet even when the drug does not cure the condition, it hardly follows that its use should be abandoned. The drug may still produce some beneficial effects at a lower dosage or in combination with other drugs whose general properties are well understood. The entire process is one of incremental adjustments in which individual feedback is immediately available and highly reliable. The one confounding problem comes from the placebo effect, which can be quite profound on people who have not received any active medications. But even in this context, the best approach may be to disclose the existence of the effect to patients and then let it operate to help them.

The possible permutations for drug use are quite varied, and it is for just that reason that the FDA should be reluctant to apply a bright line rule to keep drugs off the market. When any drug is kept from the market, regulation necessarily forecloses all the possible downstream adjustments that can be made by individual patients and their physicians in the use of particular drugs. Finding the right niche and level is standard business for countless drugs sold in the market today. Notwithstanding constant debates over its use,<sup>37</sup> Prozac remains on the market because individual physicians have had success in treating many depressive patients who have proved unresponsive to other treatments.<sup>38</sup> Steroids remain on the market even though they have a long list of adverse side effects, from weight increase to mood swings, which should daunt the most hardened potential users.<sup>39</sup> Accutane, an acne medication, remains on the market even though its potency can take the starch out of anyone, especially pregnant women for whom its use is manifestly and graphically counterindicated.<sup>40</sup> Today even thalidomide—rechristened Thalomid—is back on the market, and is extremely

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37. See, e.g., Rick Giombetti, Prozac, Suicide and Dr. Healy (Mar. 20, 2002), at <http://www.whale.to/a/prozac.html>.

38. The warnings are found at Eli Lilly & Co., Prozac.com, Safety Facts, at [http://www.prozac.com/how\\_prozac/safety\\_facts.jsp?reqNavId=2.5](http://www.prozac.com/how_prozac/safety_facts.jsp?reqNavId=2.5) (last visited Apr. 5, 2005).

39. Harm Kuipers, *Anabolic Steroids: Side Effects*, in *ENCYCLOPEDIA OF SPORTS MEDICINE AND SCIENCE* (T.D. Fahey ed., 1998), <http://sportsci.org/encyc/anabstereff/anabstereff.html>.

40. Evidence of such can be easily found on the web. See, e.g., ROCHE, ACCUTANE (ISOTRETINOIN) CAPSULES, <http://www.rocheusa.com/products/accutane/pi.pdf> (revised June 2002).

useful and profitable, among other things, for the treatment of leprosy.<sup>41</sup>

Playing with fire, then, is part of the overall picture—but the logic is inescapable. So long as downstream information is better than the generalized information in the possession of the FDA, the drug in question should be left on the market. Warnings galore can be printed on the packets and inserted in the Physicians Desk Reference. Informed consent could be required at the patient level. But the fundamental asymmetry remains. In some cases, tort liability should be added into the mix to deter the marketing of drugs without adequate warnings. The case for allowing a drug on the market is even stronger than allowing certain activities to go ahead, for example putting smoke stacks in operation, though they pose some environmental risk because of the benefits created from the activities. With drugs the self-help remedy is fully available, patients could simply not take the drug, which is not the case when pollution comes roaring through the front door. On the other hand, if the FDA bans a drug, that action allows for no second chance to correct any error in its judgment. If the FDA allows the drug on the market, there are all sorts of additional ways and opportunities to direct its use to that subset of the population that has the greatest use value.

### *C. How Safe, How Effective?*

Part of the difficulty with the FDA's approval process stems from the definition of its mission. The FDA's position was summarized in these words after the Vioxx incident:

Modern drugs provide unmistakable and significant health benefits. It is well recognized that FDA's drug review is a gold standard. Indeed, we believe that FDA maintains the highest worldwide standards for drug approval. FDA grants approval to drugs after a sponsor demonstrates that they are safe and effective. Experience has shown that the full magnitude of some potential risks do not always emerge during the mandatory clinical trials conducted before approval to evaluate these products for safety and effectiveness.<sup>42</sup>

Yet the articulation of this proposition conceals all relevant difficulties about the application of this standard. It is one thing to ask a party to illustrate that he drove on the right side of the road at the time of a collision. The line in the middle of the road is a conscientious effort to create a dichotomous universe in

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41. For data, see CELGENE PHARMACEUTICALS, THALOMID (THALIDOMIDE), <http://www.celgene.com/PDF/thalomidPI.pdf> (last visited Mar. 23, 2005).

42. *Merck and Vioxx: Putting Patient Safety First?: Hearings Before the Senate Comm. on Finance*, 108th Cong. (2004) [hereinafter *Merck Hearings*] (statement of Sandra L. Kweder, Deputy Director, Office of New Drugs, FDA).

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which actions do or do not comply with law.<sup>43</sup> The decision to allow a drug or keep it off the market might be termed “imperfectly dichotomous.” First, the decision to keep it off means that it is not used, but the decision to let it on leaves it for subsequent actors to decide. Second, no matter how hard one tries, there is no bright-line equivalent to the midline on a public highway to guide this decision. There are no drugs that are uniformly safe, and there are none that are uniformly effective.<sup>44</sup> All judgments about whether to let the drug on the market require a comprehensive kind of trade-off, which ultimately rests on questions of degree and extent. Once the true task of the mission is revealed, it becomes idle to attack the FDA whenever it lets the wrong drug on the market: It has made a calculated risk that proved, perhaps, wrong in the equation. However, once the inquiry is understood to be about trade-offs at the margin, making collective decisions to block drugs that will have use in some cases but not in others is a far larger sin. Quite simply, the misstatement of the criteria for drug permits leads to

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43. This system of clear property rights is also congruent with the strict disjunction between liability and no-liability on which a tort system works. For this reason, it is superior to the kinds of Hand formula balancing tests that require a conscious comparison of the burden of precautions with the expected benefit that they would yield. For the Hand formula’s original enunciation, see *United States v. Carroll Towing, Co.*, 159 F.2d 169, 173 (2d Cir. 1947) (Hand, J.). The most celebrated defense of this formula as a universal solvent for the tort law is Richard A. Posner, *A Theory of Negligence*, 1 J. LEGAL STUD. 29 (1972). My defense of strict liability dates back to Richard A. Epstein, *A Theory of Strict Liability*, 2 J. LEGAL STUD. 151 (1973). For a comparison of the two systems, see RICHARD A. EPSTEIN, *SIMPLE RULES FOR A COMPLEX WORLD* 92-97 (1995).

44. One exception to the basic rule involves the administration of those substances that are found naturally in the body, such as thyroxine. These substances replicate natural processes and thus are virtually foolproof, at least if added in the right dosages. See Mary J. Shomon, *All About Thyroid Drugs* (Dec. 14, 2003), at <http://thyroid.about.com/cs/thyroiddrugs/a/overview.htm> (“The conventional treatment for hypothyroidism is thyroid hormone replacement—basically, taking a prescription drug that acts similarly in the body to the human hormone thyroxine that the thyroid would normally produce.”). One possible exception to this rule has to deal with hormone replacement therapy for postmenopausal women, which has been under extensive scrutiny as of late. But there are three complications here. First, the treatment in question need not replicate the levels that the body normally produces at a particular stage in life. Rather, it may seek to increase the hormone levels above what they are in normal individuals. Second, the identified risk factors did not address the risks for women who take less than standard dosages. Third, the initial studies did not distinguish between women who started therapy before menopause from those who started later. For the original study that recommended stopping hormone replacement therapy, see Writing Group for the Women’s Health Initiative Investigators, *Risks and Benefits of Estrogen Plus Progestin in Healthy Postmenopausal Women: Principal Results from the Women’s Health Initiative Randomized Control Trial*, 288 JAMA 321 (2002). For the inevitable qualifications and complications, see Tara Parker-Pope, *Rethinking Hormones Again: Heart Risk May Be Lower in Women Who Start Early*, WALL ST. J., Oct. 12, 2004, at D1.



a fundamental misconception of the FDA mission.

This standard litany of FDA responsibilities as bracketing both safety and effectiveness also helps conceal the fundamental difference between these two statutory tests. Clinical trials are certainly part of the standard protocol, and these are customarily divided into Phase I, Phase II, and Phase III trials.<sup>45</sup> The initial concern of the Phase I trial is with basic safety: How much can patients tolerate of a new drug. Hence, the question to be answered is whether a small number of individuals can tolerate various levels of exposure so as to make it worthwhile to continue the experiment. But that said, the determination at Phase II trials (larger affairs, with different dosage levels, intended to measure safety and effectiveness in patients of the type for whom the drug is ultimately intended), and Phase III trials (often extended operations at multiple sites, dealing with both safety and effectiveness) works in different ways.

In principle, drugs should, at least in new classes, be able to demonstrate their effectiveness from relatively small groups. To be sure, in the statistical sense, a “significant” result in close cases requires a large population, which allows the investigator to determine that the two groups are not drawn from the same urn. Make that population large enough and a response difference of one percent will be statistically significant. But the *social* significance of that smallish statistical significance is another affair altogether. The additional return from that one percent increment in overall effectiveness is sufficiently small that leery patients will not willingly pay heavily for this modest improvement, either in cash or in alternative medical risks that any treatment brings in its wake. (A large effect for one percent of patients is another matter altogether.) The only significant outcomes that are worth pursuing, therefore, are those that offer eye-popping results on small populations that don’t require any refined statistical analysis for verification. In one sense, therefore, the most promising drugs in pioneer classes should be regarded as “effective” with relatively little information.

Safety, however, raises a very different set of concerns. Recall that the increased rate of heart attack and stroke in Vioxx increased from 1.9 to 3.5% in an undifferentiated user population.<sup>46</sup> Because the base rates and increments are both low, it takes very large populations, often over prolonged periods of use, to make a sensible judgment on safety issues. Yet each front-end clinical cost that is added to the mix delays the use of successful drugs as well as that of unsuccessful ones. On balance, therefore, there is a lot to be said for allowing

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45. See 21 C.F.R. § 312.21 (2004) (describing what occurs at each phase of the testing).

46. Peter Gornick & Ronald Kotulak, *Patients Calm After Merck Pulls Vioxx*, CHI. TRIB., Oct. 2, 2004, at C1. Most sources simply note that the risk of adverse consequences was about “double” without giving the numbers. See, e.g., Agovino, *supra* note 3.

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marketing after some effectiveness is established with, of course, the use of warnings to highlight the unresolved nature of the risk. The superiority of downstream individuation should not be ignored in setting the basic parameters.

*D. Using—and Stopping—Clinical Trials*

The difficulties in setting the appropriate criteria for drug marketing plays itself out most vividly in the story of an Amgen drug, glial cell line-derived neurotrophic factor (GDNF), which had been made available in clinical trials as a potential treatment for Parkinson's disease. Some individual patients had reported marked personal improvements from use of the drug, which allowed them to redo kitchens when previously they could not hold a nail stapler.<sup>47</sup> But when Amgen ran its clinical trial, it first found that the drug worked no better than a placebo on average. It then discovered that the drug carried with it serious safety risks and hazards. After reporting the information to the FDA and consulting with outside ethicists, Amgen stopped GDNF clinical trials, leaving its previous users in a lurch.<sup>48</sup> The howls of protest from unhappy patients are confirmed by the desperate measures they took before Amgen's decision was made final. GDNF is administered by a pump that injects the compound into the brain through a catheter. Many patients refused to shut down their pumps because they feared that they could not be reopened if the clinical trials had continued. The nagging suspicion is, therefore, that one reason why Amgen made this decision is the risk of liability and regulatory grief that would follow if it took any other path.

It does not take an expert to realize the genuine difficulties in interpreting the data. Some, perhaps all, of the improvement might be properly attributable to the "placebo effect" in starting any form of treatment.<sup>49</sup> But, alternatively, design flaws in the study could have reduced the effectiveness of the drug relative to its full potential. The potential side effects could be quite severe, but, then again, they were observed only in monkeys in dosages several times higher than those used in people on a brain only one-twelfth the size. The adverse effects were not found in human beings, at least to date, so the time of onset, frequency, and

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47. Andrew Pollack, *Many See Hope in Drug Pulled During Testing*, N.Y. TIMES, Nov. 26, 2004, at A1.

48. Andrew Pollack, *Patients in Test Won't Get Drug, Amgen Decides*, N.Y. TIMES, Feb. 12, 2005, at C1.

49. The placebo effect is difficult for anyone to confront because it says that people's own subjective evaluations might not supply them with the best decision. But here the solution seems to be more disclosure, not a discount of patient preferences. Let people know that they may be taking placebos. If they improve with that knowledge, then let them continue. If there is a risk of an undisclosed danger of adverse side effects from the experimental drug, then disclose that as well.

seriousness of the effects are hard to assess. Some doctors supported the use of the drug; others were against it. In light of the murky medical situation, no doubt, Amgen could be concerned about the size of the potential market for this highly controversial product. And there is, in my view, no duty for them to invest further in a drug that may promise them the unhappy trifecta of small markets, lagging profitability, and high liability exposure. But still the situation is unsettling. Suppose that the drug has a placebo effect and high risk; with full disclosure, why prevent people from taking it if they report pronounced improvements that are both undeniable and easily verifiable?

There is, of course, a now abundant line of literature that purports to supply that reason by demonstrating that individuals suffer from a myriad of cognitive biases and defects that cause them to ignore base rates and miscalculate the odds in making decisions.<sup>50</sup> No doubt all this is true, as is evidenced by the way in which the FDA structures its basic standard so as to systematically understate the benefits from earlier drug approval by ignoring heterogeneity in the user population.<sup>51</sup> But whatever the source and strength of these cognitive biases, no person should have any deep-seated emotional resistance against correcting his decisions once he obtains better information about what course of action will improve his own welfare. And these decisions are made by individuals whose feedback mechanism gives them instant information as to whether their individual condition moved to either the plus or the minus side. The implicit paternalism of allowing FDA supremacy assumes that a distant bureaucracy, which has its own institutional biases, will be a better guardian of all potential users than the people themselves.<sup>52</sup> It is often said that the ability to take risks and bear their consequences is one of the marks of a self-reliant population. The presumptions here should be set strongly in favor of allowing individuals to continue to take those drugs of choice even as other individuals, quite properly, decide to follow the opposite course of action. The decision to ingest a given

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50. See generally Daniel Kahneman & Amos Tversky, *On the Reality of Cognitive Illusions*, 103 PSYCHOL. REV. 582 (1996); Daniel Kahneman & Amos Tversky, *Prospect Theory: An Analysis of Decision Under Risk*, 47 ECONOMETRICA 263 (1979). For criticism, see Gerd Gigerenzer, *On Narrow Norms and Vague Heuristics: A Reply to Kahneman and Tversky*, 103 PSYCHOL. REV. 592 (1996). The field is dominated by two schools, which differ in the importance attached to these biases. It is easy to figure out which is which from the titles of their works. Compare, e.g., GERD GIGERENZER ET AL., *SIMPLE HEURISTICS THAT MAKE US SMART* (1999), with JUDGMENT UNDER UNCERTAINTY: *HEURISTICS AND BIASES* (Daniel Kahneman et al. eds., 1982).

51. For discussions of failures in both ordinary life and administrative agencies, see Cass R. Sunstein, *Probability Neglect: Emotions, Worst Cases, and Law*, 112 YALE L.J. 61 (2002).

52. See HENRY I. MILLER, *TO AMERICA'S HEALTH: A PROPOSAL TO REFORM THE FOOD AND DRUG ADMINISTRATION* (2000) (critiquing the FDA and urging competitive drug reviews to expedite the approval process).

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drug is the polar opposite of any public goods or collective action problem that might call for state intervention.<sup>53</sup>

*E. Upping the Baseline*

In light of these considerations, it is quite disturbing to see that the Vioxx dispute has strengthened the hand of those who think that a more restrictive set of tests should be required to let, and keep, drugs on the market. One of the worst proposals of this sort is to keep the traditional FDA protocol that stresses means to the exclusion of variance, but against a different baseline. Marcia Angell puts the proposal in the following words in speaking about Congress and the FDA:

[P]erhaps most important is what Congress has *not* done. It has not authorized the FDA to require that new drugs be tested against older ones as a condition of approval. The fact that drug companies get away with comparing drugs only with placebos is what makes it possible for the industry to live on me-too drugs. If not for that, drug companies would have no choice but to work on truly innovative drugs.<sup>54</sup>

Under this proposal the new drug will be required to beat a baseline that is established by the first entrant of its class into the market. The clear subtext to this position is twofold: These markets are not competitive in any event, and all these me-too drugs are just look-alikes anyhow, so one should just go for the lowest price.<sup>55</sup> Both of these short-term assumptions seem to be wrong. After a close examination of the market in surgical stents, Dr. Thomas Lee concluded that me-too products “reflect and create competition among drug and device manufacturers, and that competition is also a powerful driver of better quality and lower cost.”<sup>56</sup> In similar work, DiMasi and Paquette noted that the elapsed time between the first arrival of a new drug within a class and its competitors has dropped from a median of 10.2 years to 1.2 years, with greater consumer choice.<sup>57</sup>

In a deeper sense, this Angell proposal is fatally flawed because it replicates off a different baseline the same error that Malani and Hu identified in the current standard. It gives no weight to the potential variation within the subject

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53. See, e.g., MANCUR OLSON JR., *THE LOGIC OF COLLECTIVE ACTION* (1965) (detailing the under-production of public goods).

54. ANGELL, *supra* note 23, at 204.

55. *Id.* at 89-90.

56. Lee, *supra* note 21, at 211.

57. Joseph A. DiMasi & Cherie Paquette, *The Economics of Follow-on Drug Research and Development Trends in Entry Rates and the Timing of Development*, 22 PHARMACOECONOMICS 11 (Supp. No. 2, 2004).

population in cases in which there is some individuation at the user level. To be sure, the movement from zero to one drug in the marketplace may have a more positive welfare effect than the movement from one to two drugs and so on down the line. Such is a consequence of the law of diminishing returns that is applicable in all cases. But even with diminishing returns, the gain will not fall to zero and the new product in question could provide a back-up insurance if the initial product, such as Vioxx or Rezulin, is pulled off the market (often unwisely). The newer and higher standard could easily delay the introduction of any follow-on drug, even if it is in general superior in safety and/or efficacy, to any drug that was first in class, as is commonly the case.<sup>58</sup> After all, the closer the means between the two compounds, the larger the statistical sample that is needed to establish the significance. That barrier will grow with each additional entrant who must make its way over a successively higher bar.

The problems here are still more acute because the sequencing of drugs into the marketplace is by no means as clear as this model suggests. Medical research, such as that on Cox-2 inhibitors, builds on basic science research that is publicly available. It follows that multiple companies will be pursuing the same leads simultaneously. Surely in some situations it could well be that one firm gets its patent first, but the second firm is able for a variety of reasons to get its drug through the FDA more rapidly. Is it really wise social policy to require a race to have only a single winner when its consequence (since research programs are often secret) could be to force firms to play in an all-or-nothing world where tiny advantages in the laborious approval process receive huge awards for no reason?

In dealing with these issues, it is often asserted that cutting down on me-too drugs makes sense. They are said to be a social waste because they only duplicate the kinds of expenditures made by others. But this is not an argument that is distinctive to new drugs in the marketplace. Rather, it applies to all cases in which competition requires the second entrant to duplicate some expenses of the first. But that wasteful expense argument hardly justifies this conclusion. Assume, for example, that we had no FDA to check on product quality and relied exclusively on damage remedies and the rare private injunction to guard against drug failure. In that setting, no one would claim that the first entrant should be able to block all subsequent entrants from seeking to take away its market share simply because the subsequent entrant will have to incur some costs of its own. The complete response here is that the only way to eliminate all duplication in costs is to give the first entrant into every market a legal monopoly that allows it to exclude its competitors. No way.<sup>59</sup>

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58. *Id.*

59. For a defense of the competitive solution, see Mark A. Lemley, *Ex Ante Versus Ex Post Justifications for Intellectual Property*, 71 U. CHI. L. REV. 129, 135-41 (2004) (criticizing ex post

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The problem here is not new. The scope of a legal monopoly has been one of the dominant issues in the entire patent law, in which parties always fight and fret about the scope of a patent grant. The famous Supreme Court decision in *O'Reilly v. Morse*<sup>60</sup> is on point. Morse sought to claim the use of the entire electromagnetic spectrum for communicating at a distance. As the Court held, the preclusive effect would be far too great relative to any incentive needed to spur the inventive impulse.<sup>61</sup> A similar issue arises in a modern context over the question of how many different variations of a given basic molecule can be subsumed under a single patent. It is one of the perennial questions of patent law, which constantly seeks to balance the need for incentive on the one hand against the exclusionary features of the patent on the other.<sup>62</sup>

The insertion of FDA regulation does not change that issue in the slightest simply because the agency is in a position to check for safety and effectiveness. The FDA is by no means the only government agency to discharge health and safety functions. The long constitutional history of safety and health regulation has been marked by the fear that safety regulation will be used as a cloak to create a monopoly position for one of the regulated parties. To give one simple example, a rule that requires that all milk sold within a given state be pasteurized has never been construed to keep out the second entrant to the market once the initial entrant has complied with all health standards. Quite the opposite, when this issue has been squarely presented under the dormant commerce clause, any insistence that local facilities be used to meet an objective standard has been brushed aside because of the well-justified fear that the rules in question will perpetuate local monopoly power.<sup>63</sup> The key task here is to find some way in which the question of competitive balance is consistent with the overall system of regulation. And if other communities are willing to trust the health and safety of their citizens to their own regulators, there better be some strong safety reason to dispel the obvious inference that the local regulation is intended to prop up a

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justifications for not using the market system that call for centralized control).

60. 56 U.S. (15 How.) 62, 85-86 (1853).

61. *Id.*

62. See *In re Harnisch*, 631 F.2d 716, 718 (C.C.P.A. 1980) (discussing the scope of so-called Markush claims whereby different radicals are added to a standard chemical backbone). One irony is that Searle (later taken over by Pharmacia, and then Pfizer) sought to block the Merck patent on Vioxx by claiming that it was covered by an earlier Markush claim that Pfizer had filed. That claim was rejected in an exhaustive opinion in the ensuing interference action before the Patent and Trademark Office.

63. See, e.g., *C & A Carbone, Inc. v. Town of Clarkstown*, 511 U.S. 383, 394-95 (1994) (invalidating the requirement that out-of-state disposal operations ship waste through local facility); *Dean Milk Co. v. City of Madison*, 340 U.S. 349, 355-56 (1951) (striking down ostensible health justification for requiring Illinois milk producers to bottle within five miles of Madison).

local monopoly.

In dealing with the pharmaceutical industry, it is important to recognize that obtaining a patent is only the first hurdle to marketing a drug. The legal situation would become quite untenable if patent law refused to allow the patentee of an initial molecule or process to assert *Morse*-like rights over adjacent products, only to have its economic objectives undermined by the FDA's insistence that the new drug climb a higher hurdle than the previous one. The Supreme Court's dormant commerce clause jurisdiction makes *nondiscrimination* in the application of health and safety rules the touchstone of legality,<sup>64</sup> absent some very powerful showing of harm that an antidiscrimination norm cannot touch.<sup>65</sup> To be sure, the dormant commerce clause has no direct application in thinking about the proper reach of federal regulation. But the issues before the FDA are identical to those raised by state regulation. The use of a higher standard for the second and all subsequent entrants creates an indefensible form of discrimination that should not be tolerated on grounds of public policy, even if it were not the subject of constitutional challenge—which should be the case.<sup>66</sup> Using the FDA as an agent of industrial policy to exclude latecomers in the race represents an irresponsible use of public policy. The simple fact is that latecomers will always suffer a disadvantage, whether they are in a regulated or unregulated market. The newcomer will always have the first mover advantage. The private entrant that knows the effectiveness (both means and variance, across relevant subgroups) does not need to have the FDA warn it that new entry is likely to produce a meager rate of return, if such be the case. That firm can run the calculations itself to decide whether its new product could pry away enough of the market to make a difference. The only considerations that are relevant are those that turn on safety and effectiveness. Nothing about the economics of the situation suggests that the FDA should assert a strong role in keeping drugs off the market, given the other forms of regulation that are available on safety matters.

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64. See, e.g., *City of Philadelphia v. New Jersey*, 437 U.S. 617, 626-27 (1978) ("But whatever New Jersey's ultimate purpose, it may not be accomplished by discriminating against articles of commerce coming from outside the State unless there is some reason, apart from their origin, to treat them differently.").

65. See, e.g., *Maine v. Taylor*, 477 U.S. 131, 151-52 (1986) (upholding Maine's restriction on the importation of baitfish because Maine had sufficient justification, including that it threatened Maine's fisheries).

66. For my defense of the doctrine of unconstitutional conditions, see Richard A. Epstein, *The Constitutional Protection of Trade Secrets Under the Takings Clause*, 71 U. CHI. L. REV. 57, 68 (2004) (noting that the doctrine of unconstitutional conditions "places limits on the ability of the government to require individuals to waive their constitutional rights, including those to property under the Takings Clause, in order to escape the burden of some regulatory exaction") (footnote omitted).

## REGULATORY PATERNALISM IN THE MARKET FOR DRUGS

## II. DRUG WITHDRAWALS AND RECALLS

*A. What's Different About Withdrawals and Recalls?*

The discussion of the initial approval process leads to the next question, which asks how the analysis of risk and reward changes once a drug that has made its way onto the market proves to have some unwanted, and perhaps fatal, side effects. How should the FDA proceed on matters of withdrawal and recall? The most evident difference between approval and withdrawal should be in the amount of information available with which to make any considered judgment about a drug's efficacy and safety. That is, the longer the period that a drug is on the market, the more information that can be acquired about its use. Large numbers of patients using a drug for a long period of time should also lead to more reliable judgments about the individual responses to the dosages that have been supplied in particular cases. It is commonplace for independent parties to run studies that compare the effectiveness of different drugs on the market.

In light of that information, the same considerations that govern the initial permission to use drugs should apply with greater force in the withdrawal stage. If the results of a drug turn out to be disappointing, we could expect prescriptions to dwindle and the drug to be pulled, without FDA interference. But in the more common situation, the results of drug usage are likely to be varied, whereby some people benefit enormously while others do not tolerate the drug well at all. At this point the situation differs from that on original launch in only one particular: There is direct experiential evidence on whether a drug works or does not work in individual cases. The question is how that new particular alters the balance between upstream and downstream control. The better information does not, I believe, reverse the balance of convenience that was in favor of downstream control. The same difficulties with heterogeneous responses counsel against making a collective decision that precludes individual choice that is based on superior, localized information, even in the presence of serious side effects.

The political dimensions of this choice are more difficult because of the following general relationship: The more potent drugs are likely to do more good and cause more harm than less potent drugs in the same class of treatment. Given the higher variance, the action at the tails of the bell-curved distribution becomes ever more vivid. The low end of the distribution cries out for a ban, but that comes at the high cost of blocking use at the other end, where the perceived benefits will receive less attention precisely because they are less dramatic than real cases of failure—a political attention bias, as it were. That said, even with high variance drugs, with the expanded levels of drug usage it should be more, not less, possible to figure out protocols that allow the separation of patients into those who do and do not benefit from drug treatment. Here are some of the



alternatives that are open for control, but only if the withdrawal is not ordered: The drug could be made available, as is typically the case, only by prescription. The physician in turn can limit the dosage, shorten the periods of time of use, mix it with other drugs in the same or different classes, and so on. Stopping the drug always remains an option, as does starting it again after a change in diet, physical condition, or other medications. In this way, the hope is that it will be possible to preserve the use of the drug for those for whom it supplies the greatest benefit while limiting or avoiding use altogether for others.

### *B. A Tale of Two (or Three) Withdrawals*

Confirmation of these basic considerations is found by a closer look at the controversies surrounding the withdrawal of Rezulin and Vioxx from the marketplace.

#### *1. Rezulin*

In March, 1999, the FDA conducted extensive hearings over whether Rezulin should have been removed from the market.<sup>67</sup> During the course of these hearings, the persons calling for Rezulin's continued sale were not solely workers for Warner-Lambert and its affiliates. Many independent physicians and patients were quite insistent that the drug had done an immense amount of good and were adamant in their desire to continue to use it for themselves or to prescribe it to their patients.<sup>68</sup> Now it is possible to say that all these people are wrong and

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67. FDA, Endocrinologic and Metabolic Drugs Advisory Committee Meeting No. 72 (Mar. 26, 1999), <http://www.fda.gov/ohrms/dockets/ac/99/transcript/3499t1a.pdf> [hereinafter FDA Committee Meeting].

68. *See id.* Here is one statement from Dr. Robert Busch: "[W]e could fill this room with patients who have benefited from troglitazone [Rezulin]." *Id.* at 23. Also on point is the more detailed statement of Dr. Steven V. Edelman, himself a diabetic:

We know the consequences of poorly controlled diabetes: blindness, dialysis, amputations, heart attacks, strokes, depression, and unfortunately much, much more. Every day in America over 400 people die directly due to the effects of diabetes, and it's so important to look at the risk of Rezulin versus the benefits of improved glucose control when you're looking at a very serious disorder that affects the quality of life of millions of Americans on a day-to-day basis.

If one death is too many, then, yes, take Rezulin off the market, but then you must also take off glucosfos insulin, sulfonylureas, Motrin, aspirin, Tylenol, and many other medications used to treat patients with cancer and HIV.

I follow over 500 people at the Veterans' Affairs Medical Center in UCSD who are

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indeed wrong-headed in their convictions, or, worse, that they did not know that they were being harmed when they felt better, even though they knew the risks. And it is certainly possible to identify people who were hurt by the use of the drug.<sup>69</sup> But to worry about long-term consequences for persons who have to struggle day-by-day involves the supreme paternal confidence that we know far better what is good for people than they know for themselves. It is easy to make that assumption about drug use when people who are fortunate enough not to need any drug treatment at a particular time contemplate the problem in the abstract. The data always seem daunting, the medical evidence incomprehensible. But the level of comprehension radically changes when the choices to be made move out of the hypothetical realm and into choices that involve life-or-death decisions or matters of chronic pain. At this point the incentives alter. People will learn a great deal under stress and will have a very reliable feedback loop as to whether their choices are right or wrong: Do they feel better or worse? In the face of that evidence, why make the collective decision to force withdrawal of a drug when that decision makes a substantial portion of the population worse off?

2. *Vioxx*

The situation with *Vioxx* is of course different in that there was no FDA withdrawal order.<sup>70</sup> The response of the FDA was not to challenge the soundness of the Merck decision but to reassure an anxious public that its own vigilance does not end when products reach the marketplace.<sup>71</sup> But there is little reason to tarry on the question of whether the FDA should have ordered the withdrawal before Merck acted. The real question is whether the withdrawal should have been ordered at all. What follows is the FDA summary of the explanation for Merck's decision to remove the drug, which earned Merck's implicit endorsement:

6. What are the likely long-term health effects, if any, of taking this product?

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taking Rezulin therapy. You can't buy this drug back from these individuals because it has helped them to achieve and maintain control over their diabetes where previously it was not possible despite intensive efforts.

*Id.* at 24-25.

69. *See id.* The testimony of Dr. Sydney Wolfe, Director of Public Citizens Health Research Group, notes such: "[O]ur estimates of liver deaths from Rezulin up through the beginning of February of '99 [are] 43 deaths, including American and Japanese cases, from liver toxicity from this drug." *Id.* at 66-67.

70. *See supra* note 6 and accompanying text.

71. FDA, Statement on *Vioxx* and Recent Allegations and the Agency's Continued Commitment to Sound Science and Peer Review (Nov. 17, 2004), <http://www.fda.gov/bbs/topics/news/2004/NEW01136.html>.

The new study shows that Vioxx may cause an increased risk in cardiovascular events such as heart attack and strokes during chronic use.

7. What evidence supports the Public Health Advisory?

Merck's decision to withdraw Vioxx from the market is based on new data from a trial called the APPROVe [Adenomatous Polyp Prevention on VIOXX] trial. In the APPROVe trial, Vioxx was compared to placebo (sugar-pill). The purpose of the trial was to see if Vioxx 25 mg was effective in preventing the recurrence of colon polyps. This trial was stopped early because there was an increased risk for serious cardiovascular events, such as heart attacks and strokes, first observed after 18 months of continuous treatment with Vioxx compared with placebo.

8. Why wasn't the APPROVe trial stopped earlier?

The APPROVe trial began enrollment in 2000. The trial was being monitored by an independent data safety monitoring board (DSMB). It was not stopped earlier because the results for the first 18 months of the trial did not show any increased risk of confirmed cardiovascular events on Vioxx.

9. What did FDA know about the risk of heart attack and stroke when it approved Vioxx?

FDA originally approved Vioxx in May 1999. The original safety database included approximately 5000 patients on Vioxx and did not show an increased risk of heart attack or stroke. A later study, VIGOR (VIOXX GI Outcomes Research), [in patients with rheumatoid arthritis] was primarily designed to look at the effects of Vioxx on side effects such as stomach ulcers and bleeding and was submitted to the FDA in June 2000. The study showed that patients taking Vioxx had fewer stomach ulcers and bleeding than patients taking naproxen, another NSAID, however, the study also showed a greater number of heart attacks in patients taking Vioxx. The VIGOR study was discussed at a February 2001 Arthritis Advisory Committee and the new safety information from this study was added to the labeling for Vioxx in April 2002. Merck then began to conduct longer-term trials to obtain more data on the risk for heart attack and stroke with chronic use of Vioxx.<sup>72</sup>

It is useful to follow the argument paragraph by paragraph. The first point in paragraph six is of course the reason for the concern. No one should make light of the risks of heart attack and stroke and no one will; these risks are vivid and well understood by professionals and patients alike. Anyone who is convinced of the truth of this data will inquire further and discover that Vioxx does not have a

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72. See FDA, Vioxx (rofecoxib) Questions and Answers, *supra* note 5.

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clean bill of health.

The difficulties begin with paragraph seven, where the use of Vioxx 25 mg created the increased risk of cardiovascular use “first observed after 18 months of continuous treatment with Vioxx compared with placebo.” The increased risk level was from 1.9% to 3.5% in populations that are at risk generally because of age and health difficulties. But even if these numbers are dead accurate, they cut *against* withdrawal from the market, not for it. There are many people who could benefit by some combination of lower dosage and shorter usage, or possibly lower dosage and longer usage. As is so often the case with clinical studies, it is not possible to do work that plots an explicit dosage-response level so that one could compile a table that says “with an X mg pill the increased risk of a cardiovascular injury is Y.” But anyone who is armed with specific knowledge of his or her own cardiac condition can combine this background information with that personal knowledge. When appropriate, they can experiment with altering dosage patterns, switching off between Vioxx and Celebrex, or switching to other forms of painkillers. Whether it is worthwhile to take a chance on limited and altered use depends in part on the other benefits and costs of the proposed regimen. The one point that can be made for sure is that a uniform decision to stop all Vioxx on a dime need not be the best course of action for all, or even most, of Vioxx users.

Paragraph eight is defensive in tone about the decision to allow the trial to progress as long as it did, but fails to explain why the use of Vioxx is not safe for eighteen months. Nor does it address the question of how long one must remain off Vioxx or other NSAIDs before it is safe to go on them again. Lots of sensible questions, very few conclusive answers.

Paragraph nine is part of the FDA defense of its own internal processes.<sup>73</sup> But its one concrete bit of information again counsels against the removal of the drug from the market. Vioxx seems to work better for persons with serious intestinal issues. No evidence exists as to whether its use could have perhaps

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73. These processes had been subject to a scathing attack by Dr. David Graham (who was active in the Rezulin removal). *See, e.g.*, FDA Committee Meeting, *supra* notes 67, <http://www.fda.gov/ohrms/dockets/ac/99/transcript/349941b.pdf>; Merck Hearings, *supra* note 42 (statement of David Graham, Associate Director for Science, Office of Drug Safety, Ctr. for Drug Evaluation and Research, FDA). For the effective FDA rebuttal, see FDA, Statement by Dr. Steven Galson, Acting Director, Center for Drug Evaluation and Research (CDER), Regarding November 18, 2004, Committee on Finance of the U.S. Senate Hearing on Drug Safety and the Worldwide Withdrawal by Merck & Co., Inc., of Vioxx (Nov. 18, 2004), <http://www.fda.gov/bbs/topics/news/2004/NEW01138.html> (disclaiming Dr. Graham’s congressional testimony as not reflective of the FDA’s views). Nor is there any reason to set a presumption that the persons who take the most critical view of a current drug are likely to be correct. It is too risky to encourage endless escalation of judgments by giving the greatest credit to the most vocal critics.

saved the lives of the 16,000 people annually who would otherwise die from complications associated with ulcers and intestinal bleeding, but the polyps trials showed positive results for various intestinal disorders before they were halted.<sup>74</sup> Nor does the brief finding suggest that it is difficult for people to find out whether they are at greater risk for heart attacks or ulcers. But private downstream information, coupled with a good medical history, should be able to shed some real light on that question. No one doubts that there is a trade-off between Vioxx and naproxen, but this tradeoff does *not* play out in the same way in all cases. The additional warning should be able to counter the risk, given the stakes involved. There is no evidence that similar effort was used to explain the advantages of Vioxx on the label.

In short, the landscape reveals a picture in which Vioxx is better in some circumstances and worse in others. The only case in which the FDA should urge the ban is when some other drug *dominates* Vioxx on all relevant dimensions. Otherwise, downstream judgments, which seem to follow easily from the presented data, seem preferable. Yet it is quite striking that the denunciations of both the FDA and Merck do not refer to the benefit side, but simply reiterate the position that the FDA continues to operate as the “gold standard” of review, more stringent than that found anywhere else in the world.<sup>75</sup> Yet it is just that inflated view of its mission, and the unthinking assertion that higher standards for marketing approval lead to better health outcomes, that lies behind the entire misconceived mission of the FDA. There is, in practice, a massive difference between the sensible effort to prevent fraud and adulteration and the constant desire to make omnibus cost/benefit analyses, which all too often miscarry in the individual cases. In retrospect, it seems unwise to have withdrawn Vioxx given the problems that have come to light with both Celebrex and Bextra.

### 3. Celebrex

There is little reason to offer the details on the Celebrex situation (at least today) for the arguments are parallel to those with respect to Vioxx. So long as the risk is disclosed and known, any ban looks to be strongly overinclusive. Shorter periods and lower dosages of the drug may be appropriate. Indeed, if Vioxx were still on the market, some alternation between these two drugs might

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74. See Gina Kolata, *Good Pill, Bad Pill: Science Makes It Hard To Decipher*, N.Y. TIMES, Dec. 22, 2004, at A1 (“In one of the great examples of the mixed messages of science, the same study that killed the blockbuster arthritis drug Vioxx after showing that it had heart risks also found that the drug had a significant benefit: it prevented precancerous colon polyps in some patients, one of the study’s principal researchers said.”).

75. Merck Hearings, *supra* note 42 (statement of Sandra L. Kweder, Deputy Director, Office of New Drugs, FDA).

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have been a viable strategy. The calls for the return to aspirin or other NSAIDs as the painkillers of choice should not be dismissed out of hand, for it might be the appropriate response for some people. But the bleeding risks associated with its use do raise this irony: Were it not for its grandfathered status, could aspirin pass the new standards for getting on the markets if launched today? So long as downstream controls are available, Celebrex should remain on the market. Its sales may well fall in response to the new information, which is just fine; however, the total ban is not.

## CONCLUSION: VARIATION AND BENEFITS

This analysis of FDA practices should give rise to multiple sources of concern for what is, and is not, taken into account. As is evident, all adverse effects receive maximum attention and lead to a chorus that calls for caution above all. The entry of new drugs should be slowed, greater supervision should be given to drugs that are already on the market, and strong products liability, fraud and breach of warranty suits should be pressed into service to back up the regulatory apparatus. This evident social consensus helps explain the reactions to both Vioxx and Celebrex, and seems in many cases to be supported by that oldest of medical maxims, *primum non nocere*, first do not harm. But unfortunately, the relevant considerations make it clear that this maxim—or any akin to it, such as “better safe than sorry”—does not capture the full set of relevant considerations in any cost/benefit analysis applicable to pharmaceutical products. Gains in these cases matter as much as losses, and members of the public are not “safe” if public policy causes the failure to get some new, albeit risky, therapy, and this failure results in serious impairments followed by death. In dealing with serious medical questions, there is no risk-free alternative that acts as the baseline from which these time-honored maxims can take place. It is dreaming to think that any upstream federal drug policy can eliminate risk. Necessarily, there is harm in *not* giving risky drugs that are beneficial just as there is harm in giving potent drugs with devastating side effects. Both kinds of error are always in the mix.

In light of this simple but sober truth, this nation should rethink its basic drug policy on all three matters discussed herein. So long as benefits count and so long as individual responses to standard treatments vary, individualized downstream determinations should trump standardized government calculations. The current call for reform finds an easy target when it takes the stance that whatever is good for the drug houses is bad for the American people. But that statement makes no more sense today than Engine Charlie Wilson’s famous remark of fifty years ago: “What’s good for the country is good for General Motors and vice versa.” Unfortunately, the world is a messier place than either of these bromides suggest. Sometimes social welfare aligns with the release and use of new drugs, sometimes not. More often, it is the former, not the latter, so long

as individual choice is available. Our pharmaceutical paternalism comes at a very high price, and we make a major mistake when our regulatory system sets its face against the introduction of new drug therapies. As the old song says, you always hurt the ones you love.

#### EPILOGUE

It is always dangerous business to write a scholarly article about an issue that is in full flux. That proposition has proved itself time and again during the revisions of this Article on the proper role for the FDA. The final revisions of this Article took place just after an advisory panel to the FDA recommended that Bextra, Celebrex, and Vioxx be left on the market. On April 7, 2005, the FDA confounded most observers by going beyond the recommendation of its panels. It requested that Pfizer remove Bextra from the marketplace and that black box warnings be put on Celebrex and a long list of NSAIDs.<sup>76</sup>

In the FDA's brief advisory, it gave this explanation for its decision:

In reaching these decisions, FDA has carefully considered the available data on all of the NSAIDs. The Agency has also considered presentations, discussions, and votes from the joint public meeting of the FDA Arthritis Advisory Committee and the Drug Safety and Risk Management Advisory Committee held on February 16, 17, and 18, 2005 to discuss the CV safety concerns for these drugs along with their overall risk-benefit.<sup>77</sup>

Which is to say, it gave no explanation at all. Nothing in its actions leads me to change my views. Unfortunately, I fear that no reasoned argument will lead the FDA to reconsider its views. My Article stands as is.

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76. FDA, Public Health Advisory, FDA Announces Important Changes and Additional Warnings for COX-2 Selective and Non-Selective Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) (Apr. 7, 2005), <http://www.fda.gov/cder/drug/advisory/COX2.htm>.

77. *Id.*